CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-081

MEDICAL REVIEW(S)

NDA 21081 – HOE 901
LANTUS (glargine insulin)– submitted by Hoechst Marion Roussel (HMR)

Medical Officer's Review

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HFD 510

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(Revised January 24, 2000)

APPEARS THIS WAY
ON ORIGINAL

Background:

HOE 901 is a synthetic insulin analogue in which two arginines are added to the carboxy-terminus of the B chain. Addition of these two basic amino acid residues makes the molecule relatively insoluble at physiological pH. HOE 901 is dissolved at pH 4, comes out of solution when injected, and is absorbed slowly from the injection site. It is reported to maintain constant activity for 24 hours after a single injection. HOE 901 was designed to compete with NPH insulin, which is now the major insulin formulation that diabetic patients take as "basal" insulin. The absorption of NPH is highly variable. It is generally considered to have a maximal effect at about 4-12 hours after injection and to be largely dissipated by 24 hours. Patients with type 1 diabetes use both basal insulin (NPH or Lente; Ultralente is rarely used) and short acting insulin (regular or Lispro). One common regimen is to take a single injection of NPH in the evening and 3-4 injections of regular or lispro before meals. A second popular, but less intensive, regimen is twice daily NPH (roughly 2/3 in the morning and 1/3 in the evening) with supplemental injections of regular insulin or Lispro as needed. There are numerous variations on these two major strategies.

NPH insulin is given either once per day or twice per day. HOE 901 was designed to be given once per day. A fair comparison required that HOE 901 be tested against BOTH once daily and twice daily NPH. This feature was incorporated in the design of the phase 3 studies. HOE 901 was always given at bedtime. NPH was given at bedtime in the once daily regimen or at bedtime and in the morning in the twice daily regimen. Whether patients received once or twice daily NPH was largely determined according to their previous experience with insulin treatment. Based on their usual practice, some centers declared in advance that they would use the twice-daily regimen or the once a day regimen. Some centers used both regimens. Patients previously on multiple doses of basal insulin were generally treated with twice daily NPH during the study, while those previously on once daily basal insulin received once daily NPH. Studies were unblinded because HOE 901 is a clear solution while NPH is a suspension. Prior to injection, patients need to verify that the HOE 901 solution is clear and that the NPH is uniformly suspended. Blinding would therefore not be medically appropriate and sham injections would have severely limited the ability to recruit volunteers.

Lack of blinding of study medications should put a limit on the types of comparisons that are made and the inferences drawn from those comparisons. GHb (glycohemoglobin) is an objective laboratory measurement that reflects plasma glucose levels over several months. In the absence of any change in insulin dose, lack of change in GHb level in patients with type 1 diabetes is a reasonable indication that two insulin preparations are therapeutically equivalent. Differences in frequency of hypoglycemia are not reliable because reporting of hypoglycemia is subject to bias. Given that HOE 901 and NPH have different absorption time profiles, it is not surprising that differences might exist in the diurnal peaks and valleys of plasma glucose concentration. The Sponsor has performed many analyses in an attempt to show that treatment with HOE 901 leads to less hypoglycemia than NPH. In the absence of documentation by a severe and objective event, such as seizure, coma or hospitalization, I do not believe that analysis of patient-

generated reports of hypoglycemia should be used to support a labeling claim. For the sake of discussion, I have included in my review the 'p' values from the statistical analysis performed by the Sponsor. However, I do not agree that this type of analyses is appropriate given the limits of the study design.

The Sponsor submitted three amendments in response to questions raised during the review. Amendment 1 was submitted October 18, 1999 and dealt with concerns about the potential for HOE 901 to exacerbate diabetic retinopathy. Amendment 2 and 3 were submitted December 2 1999, and January 13, 2000 respectively in response to questions about in methods for measuring insulin action in vitro and assaying insulin antibodies.

Studies in type 1 diabetes NOTE: FPG of 10 mM=180 mg/dl

3001 - use in combination with regular insulin

This was a 28-week study comparing HOE 901 to NPH insulin. Patients were required to have C peptide negative type 1 diabetes, to have used insulin continuously for at least one year, and to have GHb < 12.1%. Exclusion criteria were pregnancy or child bearing potential without adequate contraception, surgical treatment for diabetic retinopathy within three months, use of other glucose-lowering drugs within 4 weeks, impaired renal function (creatinine > 2 mg/dl) or abnormal liver tests (transaminase > 2x ULN). The 28 weeks controlled observation was preceded by up to four weeks of run-in during which time patients continued their usual insulin regiments. Patients were familiarized with the OptiPen/Hoechst and ———————— glucose meter. All insulins were given using 3-ml cartridges. The goal of titration was fasting blood glucose (FBG) of 80-120 mg/dl. Basal insulin was increased by at least 10% (not to exceed 4 units) for FBG > 120 mg/dl not more frequently than every two days. Dose decreases were made as medically required because of hypoglycemia. Regular insulin was injected before each meal. The dose depended on the usual practice of the patients. The goal was to achieve pre-meal

glucose levels of 80-120 mg/dl. The primary measure of efficacy was change in GHb. Secondary measures were change in FPG on clinic visits and FBG measured at home. Hypoglycemia was defined by blood glucose under 50 mg/dl and classified as symptomatic or asymptomatic. Severe hypoglycemia was defined in accordance with the DCCT to be hypoglycemic events requiring the assistance of a third party, with glucose < 50 mg/dl or prompt recovery with oral carbohydrate, iv glucose or glucagon. To assess changes in diabetic retinopathy, fundic photographs were taken at baseline and at the end of the study. They were taken every 12 weeks in patients with moderate nonproliferative retinopathy (ETDRS level 43)

292 patients were randomized to receive HOE 901 and 293 to receive NPH. They were about 56% male, and 99% white with a mean age of 39.2 years. The mean age of diagnosis of diabetes was 23.7 years. The mean duration diabetes was 15.5 years with 14.9 on insulin. 51% had been taking basal insulin once daily and 49% had been taking two or more injections of basal insulin. Mean baseline GHb of the ITT population was 7.9% and mean FPG was 12.4mM (223 mg/dl). There were no differences between the HOE 901 and NPH group with respect to these demographic characteristics. There were 16 withdrawals in the HOE 901 group and 21 in the NPH group.

Changes in insulin dose over the course of the study were very small. Patients on NPH (all regimens) started with a mean total insulin dose of 49 units, 21 basal and 28 regular. There was no change over the study. Patients on HOE 901 started with a total dose of 46 units, 20 basal and 26 regular. The dose of total insulin decreased by 2 units and the dose of basal insulin decreased by one unit. No change was reported in the dose of regular (I assume that data was rounded off to the nearest unit to account for the arithmetic discrepancy, even though the figures are presented to the nearest 0.1 unit). When one examines the change in insulin dose according to patients' prior insulin regimen, one sees that patients switched from once daily NPH to once daily HOE 901 had to decrease their dose of basal insulin by 3 units from an initial dose of 22 units. Otherwise there appeared to be no differences. See Table 3001/ 6.8.1

Median daily insulin dose (IU) during treatment by prior basal insulin regimen

	Prior once daily			Prior more than once daily		
	Total insulin	Basal insulin	Basal/ Total	Total insulin	Basal insulin	Basal/ Total
HOE 901						
N	150	150	150	137	137	137
Baseline	46.0	17.0	0.38	46.0	22.0	0.50
Change from baseline To endpoint	-1.0	0.0	0.01	-2.0	-3.0	-0.05
NPH		NPH once daily			NPH twice daily	
N	126	127	126	119	122	119
Baseline	51.0	20.0	0.40	46.0	22.0	0.47
Change from baseline To endpoint	0.0	0.0	0.00	1.0	1.0	0.01

Change in GHb was the primary measure of efficacy. As shown in table 7.1.1 below, there were no differences between HOE 901 and NPH, either with respect to baseline or change at endpoint. The only differences is that patients previously at multiple daily injections of basal insulin (mostly NPH) had lower GHb values at baseline (about 7.7%) than patients who had previously been taking basal insulin once daily (about 8.1%). This is worth noting because it illustrates that once daily NPH is not as good a regimen as twice daily, even though a once daily regimen is commonly used.

Change in GHb by prior basal insulin regimen (%)

	Prior once daily basal regimen		Prior more than once daily basal regimen	
	HOE 901 Mean (N=71)	NPH once daily Mean (N=66)	HOE 901 Mean (N=230)	NPH twice daily Mean (N=237)
Baseline	7.28	7.77	7.68	7.69
Change from baseline to endpoint	-0.17	-0.31	-0.03	-0.05

There was little difference between the two insulins in glucose measurement. There was a statistically significant reduction in self monitored fasting blood glucose with HOE 901 at week 28, but this was not confirmed with laboratory determination of plasma glucose at week 28. The average of 8 determinations of blood glucose was lower for NPH at week 20 but not at weeks 8 or 28. With respect to subgroup analysis, there were no differences with respect to gender or duration of diabetes. Only 2.4% of patients were

over 65 years old so that potential differences due to age could not be adequately assessed.

The rate of symptomatic hypoglycemia (average number of events per patient per 28 day period) was higher (p=0.033) for HOE 901 (3.96) than for NPH (3.40) for the first month of treatment but was not different for the remainder of the study. Patients on once daily NPH had clustering of hypoglycemia between 2:00-4:00 am while patients on HOE 901 had hypoglycemia events throughout the day. 73.3% of patients had at least one episode of symptomatic hypoglycemia during the first month of HOE 901 compared to 67.6% of patients on NPH (p=0.079) but there was no difference for the rest of the study. There were no statistically significant differences between HOE 901 and NPH with respect to severe hypoglycemia, but the trend was in favor of HOE 901. Of severe hypoglycemia confirmed by glucose < 2 mM, there were 11/292 (3.8%) of patients on HOE 901 compared to 20/293 (6.8%) on NPH (p=0.11). Among patients previously on once daily basal insulin, severe hypoglycemia occurred in 17/153 (11.1%) of patients on HOE 901 compared to 29/147 (19.7) of patients on NPH. There were a total of 39 episodes in HOE 901 patients compared to 79 episodes in the NPH patients (table 47). HOE 901 appeared better than either once daily or twice daily NPH in these patients. Among patients who had previously been on multiple doses of basal insulin, there were no statistically significant differences, but patients on twice daily NPH tended to have less hypoglycemia than patients on HOE 901. All symptomatic hypoglycemia occurred in 92.1% of HOE 901 patients compared to 85.4% of NPH patients (p=0.096) (data from table 51).

There was no difference in injection site reactions between HOE 901 and NPH. A 20% absolute rise in rise in insulin binding to antibodies was reported in 8 patients on HOE 901 and one patient on NPH. All nine patients had increased in binding both to radiolabeled HOE 901 and insulin. The most dramatic rise occurred in HOE 901 patients 3160/2811. At baseline this patients serum bind of HOE 901 was 7.15% and for human insulin was 6.19%. After treatment with HOE 901, binding increased to 77.15% and 75.09% for HOE 901 and human insulin respectively. However the patient's total insulin dose decreased 40 and 34 units, while GHb remained unchanged at 6.5%. Changes in E Coli antibodies were also non-illuminating. 5 patients became positive in the HOE 901 group compared to 7 patients in the NPH group. A change from positive at baseline to negative at endpoint was detected in 1 patient on HOE 901 and 5 patients on NPH.

Conclusions: Glycemic control with HOE 901 is largely the same as with NPH, except that patients switched to HOE 901 had more hypoglycemia during the first month than patients continued on NPH. Extensive subgroup analysis yielded minor differences with respect to hypoglycemia: patients previously on once daily basal insulin appeared to have less hypoglycemia if treated with once daily HOE 901 than once daily NPH. However, patients previously on multiple doses of basal insulin tended to have less hypoglycemia if continued on twice daily NPH than switched to once daily HOE 901.

Study 3004 – Use in combination with regular insulin ——

This was a 28 week open label multicenter comparison of HOE 901 with NPH insulin in patients with type 1 diabetes. Patients were stratified based on their previous insulin regimen of once daily or more than once daily basal insulin. Patients previously on once daily basal insulin were randomized to once daily NPH ——) or once daily HOE 901. Patients on multiple doses of basal insulin previously were randomized to twice daily NPH ——) vs once daily HOE 901. Patients were enrolled with typical type one diabetes (C peptide under 1.5 ng/ml) who had been on insulin for at least one year. HOE 901 was supplied in 5-ml vials. —— NPH and regular human insulin were supplied as 10-mg vials. HOE 901 was given at bedtime. NPH insulin was given at bedtime or at bedtime and in the morning. The insulin regimen was based on the patient's previous regimen. But investigators were told in advance that a 10% reduction in HOE 901 dose had previously been observed to decrease the risk of nocturnal hypoglycemia in patients previously on multiple basal insulin regimens. Insulin dose was titrated with the goal of attempting to keep the fasting and premeal blood glucose between 80-120 mg/dl and the bedtime blood glucose between 100-144 mg/dl. In-patient plasma glucose monitoring was done at selected sites.

Patients treated were 534 total (270 males and 264 females), 264 on HOE 901 and 270 on NPH. The average age was 38.5 years; average age of onset of diabetes was 21.5 years. Average duration of diabetes was 17.4 years with duration of insulin treatment, 17.2 years. Mean values at baseline were GHb 7.7%, FPG 11.8mM and FBG mM. Once daily basal insulin had been used previously by 26.6% of patients, twice daily by 71.4% and three times daily by 2.1%. There were no baseline imbalances among treatment arms.

Mean insulin dose went up slightly (1.8 unit's basal and 1.7 unit's regular) in patients on NPH. In patients on HOE 901 there was a shift from basal to regular in patients who had previously been on multiple doses of basal insulin. By contrast, patients who had previosuly been on once daily basal insulin showed a small increase in basal and small decrease in regular.

Change from baseline to endpoint in insulin dose (units) for patients on HOE 901

	Previous once daily basal	Previous multiple daily basal
Baseline basal insulin	19.2	32.3
Change	+4.5	-7.1
Baseline regular insulin	33.9	17.3
Change	-1.7	+5.9

(taken from 6.8.1)

Mean GHb was about 7.7% at baseline in all groups. Mean reduction from baseline was 0.42 and 0.10 for patients on HOE 901 previously on once daily or multiple basal insulin

respectively, and 0.29 and 0.19 for patients on NPH previously on once daily or multiple doses of basal respectively. Frequency of symptomatic hypoglycemia was lower for patients on HOE for month 2- endpoint, expressed either as all symptomatic hypoglycemia (86.8% vs 91.4%, p=0.66), nocturnal hypoglycemia (18.2% vs 27.1%, p=0.01) or symptomatic hypoglycemia documented with BG< 2.0 mM (39.9% vs 49.2%, p=0.02). The difference between HOE and NPH in nocturnal hypoglycemia was greatest for greatest for patients who had previously been on once daily basal insulin. But the difference with respect to all confirmed hypoglycemia was greatest for patients who had been on multiple doses of basal insulin. The frequency of severe symptomatic hypoglycemia from 2 months to endpoint was 1.9% in HOE 901 patients compared to 5.6% of NPH patients (p=0.012). With respect to asymptomatic hypoglycemia, HOE 901 was inferior to NPH.Glucose values under 2.8 mM were reported in 33.3% of patients on HOE 901 compared to 19.6% of patients on NPH(p=0.0005). Glucoses under 2 mM were reported in 8.7% of patients on HOE 901 compared to 3.0% of patients on NPH (p=0.005). The difference between the two treatments in asymptomatic hypoglycemia was confined entirely to patients who had previously been on multiple basal insulin. Glucose values under 2 mM were reported in 10.3% of these patients who received HOE 901 compared to 2.5% of patients who received NPH (p<0.05). Among patients previously on once daily basal, this degree of asymptomatic hypoglycemia was reported in 4.3% of patients on HOE 901 and 4.2% of patients on NPH.

There was on episode of sudden death in a patient on NPH. Serious AE's were reported in about 13% of patients in both groups, possibly related to study drug in about 8.5% in both groups. There were two HOE 901 patients hospitalized because of hypoglycemia and one NPH patient.

Dropouts were 31 on HOE 901 and 22 on NPH. On HOE 901, 8 patients (3%) dropped out because of an adverse event compared to 1 with NPH. In one HOE 901 patient the cause was severe hypoglycemia. Five patients in each group had allergic reactions with rash and/ or urticaria. Two were described as "severe" with NPH but no patients were withdrawn from this study. Injection site pain thought the be related to study medication occurred in 9 patients on HOE 901 and one patient on NPH. Five patients on HOE 901 and three on NPH had increases in antiinsulin antibodies of 20% (total increase) or more. The most dramatic case was a HOE 901 patient whose antibody binding were about 13% for both drugs at baseline and was 77% at endpoint. Despite this rise in insulin binding the patient's clinical picture was remarkably constant. The total insulin dose fell from 26 units to 24 units. GHb was 8.0% at baseline and 8.2 at endpoint.

Antibodies to E Coli changed from negative to positive in 6 patients on HOE 901 and 7 on NPH. 16/264 HOE 901 patients and 17/270 NPH patients were positive at baseline and endpoint.

A three step or greater progression of retinopathy occurred in 3.2% of HOE 901 patients and 3.9% of NPH patients. Clinically significant macular edema was reported in 0.9% of HOE 901 patients and 1.3% of NPH patients.

Patients in both groups gained a mean of about 0.8 kg. There was no difference between the two treatments. Neither were there differences with respect to vital signs and laboratory or EKG abnormalities. One patient on HOE became pregnant. Total exposure to HOE 901 was 41 days of pregnancy. The baby was born healthy (amendment 2)

Summary: Glycemic control is largely the same with HOE 901 and NPH. Patients previously on multiple doses of basal insulin experience a shift of about about 20% of their insulin dose from basal to regular when they are switched to once daily HOE 901. Reporting of hypoglycemia was variable depending on definition and subgroup.

Study 3005 – Use in combination with insulin lispro

This was a 16-week open label study, conducted in the USA and Canada, comparing HOE 901 to NPH insulin, when used in combination with insulin lispro, in patients with type 1 diabetes. HOE 901 was supplied in 5 ml vials. Lispro and NPH insulin were supplied as 10 ml vials. Patients randomized to HOE 901 were told not to mix HOE 901 with lispro. No specific instructions are described for patients randomized to NPH. Insulin Lispro was given 0-15 minutes before each meal " according to the subject's customary regimen." The study design was similar to 3001 except that patients "were stratified by their prerandomization NPH insulin regimen, once versus twice daily. Then, within each stratum subjects were randomized to 1 of the 2 treatment groups(HOE 901 or NPH insulin)." In addition, investigators were told the results of a preliminary study in which "it appeared the occurrence of nocturnal hypoglycemia was less when the HOE 901 doe was lowered approximately 10% in subjects (previously) using NPH twice daily."

588 patients completed the study, 295 on HOE 901 and 293 on NPH. There were 31 dropouts, 15 on HOE 901 and 16 on NPH. 'Adverse event" was the reason in 2 patients on NPH and none on HOE 901. "Lack of efficacy" was the reason in 2 patients on NPH and none on HOE 901. "Subject did not wish to continue" was the reason in 10 patients on HOE 901 and 5 patients on NPH. Demographic characteristics among treated patients were as follows: 50.6% were male. The mean age was 39.2 years and mean BMI 25.6 Mean age of onset of diabetes was 21.3 years. Mean duration was 18.5 years with 18.2 on insulin. Mean GHb at baseline was 7.6%, mean FPG was 12.0 mM and mean FBG was 9.6mM. There were no differences between patients treated with HOE 901 and those treated with NPH.

The dose of basal insulin at baseline was 28.4 units in patients treated with HOE 901 and 28.3 units in patients treated with NPH. The mean dose of basal insulin fell 4.5 units in patients treated with HOE 901 and rose 0.9 units in patients on NPH. The mean dose of Lispro rose by 1.5 units in HOE 901 units and fell by 0.5 units in patients on NPH. Patients who had previously been on multiple doses of basal insulin but who switched to

HOE 901 accounted for the difference in dose adjustment between HOE and NPH. These patients started with a mean basal insulin dose at baseline of 31.5 units, but the dose was reduced by 6.5 units after one week (median reduction 5.0 units) and by 6.1 units at the end of the study. By contrast, patients previously on multiple dose basal insulin, and whose study medication was twice daily NPH, had a mean dose of basal insulin at baseline of 30.8 units which was reduced by only 0.7 units at the end of study in patients on HOE 901 In compensation for the changes in basal insulin, the mean dose of Lispro rose by 3.1 units in patients on HOE 901 and fell 0.3 units in patients on twice daily NPH. (see 3005 table 6.8.1)

Change from baseline to endpoint in mean basal, regular, total insulin dose and the ratio of basal/total insulin dose

			Prior once daily basal regimen		Prior more than once daily basal regimen	
Insulin	**Total HOE 901**	**NPH all regimens**	**HOE 901**	**NPH once daily**	**HOE 901**	**NPH twice daily**
Basal insulin						
N	307	308	71	69	236	239
Baseline (IU)	28.4	28.3	18.3	19.6	31.5	30.8
Change from baseline (IU)	-4.5	0.9	0.9	1.8	-6.1	0.7
Insulin lispro						
N	305	302	71	69	234	233
Baseline (IU)	22.1	22.2	27.5	31.4	20.4	19.5
Change from baseline (IU)	1.5	-0.5	-3.6	-1.0	3.1	-0.3
Total insulin						
N	305	302	71	69	234	233
Baseline (IU)	50.3	50.4	45.8	51.0	51.7	50.2
Change from baseline (IU)	-2.9	0.3	-2.7	0.8	-2.9	0.2
Basal/total						
N	305	302	71	69	234	233
Baseline (IU)	0.567	0.560	0.407	0.388	0.616	0.611
Change from baseline (IU)	-0.060	0.014	0.042	0.026	-0.091	0.010

There was no difference between HOE 901 and NPH with respect to the primary analysis of efficacy which was change in GHb from baseline to endpoint. Mean baseline GHb was 7.6% in HOE 901 patients compared to 7.7 in NPH patients (p=0.27) . The change in baseline was – 0.07 for HOE 901 patients compared to –0.08 in NPH patients (p=0.84).

As shown in table 7.1.1, the data for the two treatments is virtually identical for the patients who had previously used multiple doses of basal insulin. However, for patients who had previously been on once daily basal insulin, there was an apparent imbalance at baseline with patients on HOE 901 having a somewhat lower value of 7.28% (SE 0.14, n=71) than the value of 7.77 (SE 0.12, n=66) for patients treated with NPH. That the change in GHb was somewhat greater with NPH (-0.31) than for HOE 901 (-0.17) is probably not a real difference. (table 7.1.1)

Mean GHb (%) values based on prior basal regimen

Timepoint	Prior once daily with basal insulin		Prior more than once daily with basal insulin	
	HOE 901 (N=146)	NPH once daily (N=121)	HOE 901 (N=137)	NPH twice daily (N=121)
Baseline	8.08	8.13	7.68	7.80
Change from baseline to endpoint:	0.20	0.10	0.28	0.16

Symptomatic hypoglycemia was reported at least once by 90.6% of patients on both study treatments. Events confirmed by blood glucose < 2 mM was reported by 31.6% of patients on HOE 901 compared to 33.3% on NPH. The rate of hypoglycemia (events per patient per 28 days) over the course of the study was also not different. However, the rate of symptomatic hypoglycemia during the first month of treatment was higher in HOE 901 patients than NPH patients (4.0 vs 3.0; p=0.0085) The time to first hypoglycemia event was also earlier for HOE 901 than for NPH (4.0 days Vs 6.0 days, p=0.0595). The frequency of nocturnal hypoglycemia was also greater for HOE 901 than for NPH. Over the entire study, 69% of HOE 901 patients and 63% of NPH patients (p=0.057) reported nocturnal hypoglycemia. During the first month the frequency also tended to be greater for HOE 901 patients (44.5% vs 38.8% p=0.092). The rate of nocturnal hypoglycemia events per 28 days over the entire study was also higher for HOE patients (0.47 vs 0.26 p=0,023), but most of the difference occurred early in treatment. The median time to first episode was 35 days for HOE 901 compared to 52 days for NPH (p=0.064). Among patients previously on once daily basal insulin, nocturnal hypoglycemia confirmed by BG < 2.0 mm occurred in 4.1% of patients on HOE 901 during the first month compared to 1.4% of patients on NPH. This difference did not exist for the remainder of the study or for patients previously on multiple dose basal insulin. Asymptomatic hypoglycemia with BG, 2.8 mM was more frequent in HOE 901 patients than NPH patients (19.4% vs 13.3%, p=0.0165).

Mean fasting plasma glucose was about 12 mM at baseline. The fall was consistently greater in HOE 901 patients than in NPH patients The difference between the two treatments was 1.58 mM (p=0.0001) at 4 weeks and was maintained at endpoint difference of 1.64mM. This difference was confirmed by self monitoring fasting blood glucose values. The mean baseline value was about 9.6 mM. The fall was greater in HOE 901 than NPH patients by 0.96 at endpoint and throughout the study. Day to day variability of FBG was lower in HOE patients but this was not confirmed using plasma glucose. The fall in average plasma glucose tended to be about 0.6 mM lower in HOE patients but this did not achieve statistical significance.

Treatment emergent adverse events were reported in 80.6% of patients on HOE 901 and 76.4% of patients on NPH. Although seemingly unrelated to treatment, the four most frequently reported AE's, upper respiratory infection, accidental injury, infection and headache, all were reported somewhat more frequently in patients on HOE 901 than NPH (30.3, 10.6, 9.7 and 9.0% compared to 24.6, 7.4, 6.5, 6.5%). As has been discussed in detail above, hypoglycemia was reported as an AE in 28 patients (6.8%) on HOE 901 and 20 patients (5.2%) on NPH. It is also worth noting that there were six patients on HOE 901 compared to 1 patient on NPH who had a hypoglycemia event possible related to taking Lispro by mistake instead of the test drug The only glaring difference between the two treatments was injection site pain which was reported in 20 (6.5%) patients on HOE 901 compared to 1 (0.3%) of patients on NPH.

There were no deaths in the study. Two patients on NPH had hypoglycemic events, which were assessed by the investigator as life threatening. This is the only AE requiring hospitalization that was considered to be study-drug related. Hospitalization occurred in 7 other patients on HOE 901 and 10 other on NPH. Although not classified as possibly related to study drug, it should be noted that one patient on NPH was hospitalized because of hyperosmolar coma and one NPH was hospitalized because of ketoacidosis. I do not see evidence that any of the hospitalization for HOE 901 may have been misclassified. No patients on HOE 901 withdrew because of an AE. One patient (163/6) on NPH withdrew because of hypoglycemia as already noted. A second patient on NPH withdrew because of cancer of the pancreas. Unexplained rash/pruritis was reported in 4 patients on HOE 901 and 3 patients on NPH.

A 20% absolute increase in insulin antibodies was reported in 7 patients on HOE 901 and none on NPH. The most dramatic of these seven cases, 181/3 had HOE 901 antibodies of 7.28% before treatment and 63.78% at endpoint. Antiinsulin binding was 6.89 at baseline and 41.89% at baseline. Despite this dramatic increase in binding, total insulin dose only rose from 36 to 38 units and GHb fell from 7.7% to 6.9%. In the remaining six cases, the rise in insulin binding was associated with a fall in insulin dose and little change in GHb. 1 HOE901 patient and 8 NPH patients who were negative for E Coli antibodies at baseline were positive at endpoint.

Two patients on NPH developed clinically relevant ECG changes. Two patients on HOE 901 became pregnant. One patients had an abortion. The outcome of the second pregnancy is not known.

Summary: Glycemia control was similar with HOE 901 as with NPH. Mean GHb was slightly lower in the HOE 901 patients at baseline but the change was the same on both treatments. Reporting of hypoglycemic events was statistically greater with HOE 901 but this difference was not reflected in greater hospitalizations or dropouts due to hypoglycemia. A 20% reduction in dose of basal insulin occurred in patients switched to HOE 901 from multiple injections of basal insulin. This decrease in basal insulin was partially offset by an increase in Lispro. An error in taking Lispro instead of study insulin is believed to have occurred in six patients on HOE 901 and one patients on NPH.

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Pediatrics:
This was a 28 week open-label randomized controlled study comparing HOE 901 to NPH insulin in patients ages 6-15 with type 1 diabetes who had been treated with insulin for at least one year and had HbA1c of < 12%. Prior to randomization patients were taught how to use a standard glucose meter and to self-administer insulin with a Hoechst pen. Patients were randomized based on whether they were using NPH twice per day or once per day. HOE 901 was administered once per day in the evening (19:00-22:00). Patients received NPH either once per day in the evening (19:00-2200) or twice per day in the evening and morning (before breakfast). Some centers offered both once daily and twice daily NPH based on patients' preference. Other centers offered only one regimen or the other. The dosage of basal insulin (HOE 901 or NPH) was titrated to try to keep the FBG under 160 mg/dl. All patients received regular insulin boluses prior to meals. The goal was to try to keep the pre-meal glucose between 80-160 mg/dl. The primary measure of efficacy was change in HbA1c. Secondary measures of efficacy were home-measured glucose levels and frequency of hypoglycemia. Severe hypoglycemia was defined according to DCCT criteria of neurological changes of sufficient severity to require the assistance of a third party, which were consistent with hypoglycemia and accompanied by a glucose level under 50 mg/dl or prompt recovery with administration of glucose or glucagon.

Of the 349 patients randomized, 174 received HOE 901 and 175 received NPH (once daily in 114, twice daily in 61) The average age was 11.7 years. The median age was 12 years. The age range among HOE 901 patients was 5-15 and for NPH patients was 5 – 16. The average age of onset of diabetes was 7.4 years. The mean HbA1c at baseline was 8.7% and FBG was 10.8 mM. . There was a small M/F imbalance. 55.7% of the HOE 901 patients were male compared to 48% of the NPH patients. 59% of patients had previously received once daily NPH insulin. 41% had been receiving twice daily NPH insulin.

Mean baseline HbA1c was slightly lower in HOE 901 patients than in NPH patients (8.48% vs 8.81%, p=0.04). The mean reduction in HbA1c was 0.28 % in patients on HOE 901 compared to 0.27% in patients on NPH. There was little change in insulin dose over the study. The median baseline total insulin dose in HOE 901 patients was 40 units. The median increase was 2 units. The median total insulin dose at baseline was 37 units for NPH patients. The median increase was 4 units. For HOE 901 patients the small increase in total insulin dose was accounted for by an increase in regular insulin. In NPH patients, there were small increases in both basal and regular insulin. The only clinically important point related to change in insulin dose is that HOE 901 patients who previously had been on twice daily NPH decreased their dose of basal insulin by 5 units (median value) and increased their dose of regular by 4 units. Patients continued on twice daily NPH increased the dose of basal insulin by 6 units and increased their dose of regular insulin by 4 units. Patients continued on once daily basal insulin showed little dose adjustment.

Symptomatic hypoglycemia was reported in 79% of patients in both groups. Symptomatic hypoglycemia with documentation of BG< 2 mM was reported in 30% of patients on HOE 901 and 28% of patients on NPH. The small excess in symptomatic hypoglycemia in the HOE 901 group was due to increased reporting during the first month among patients who had previously been on once daily NPH. Severe symptomatic hypoglycemia occurred in 23% of HOE 901 patients compared to 29% of NPH patients, but documented BG <2mM was present in 9.8% of HOE 901 patients compared to 9.7% of NPH patients. Seizure, coma or syncope was reported in 4.6% of patients on HOE 901 (13 episodes) and 2.9% of patients (6 episodes) on NPH. One patient on HOE 901 had six episodes of syncope. Asymptomatic hypoglycemia with BG <2.8 mM was reported in 27% of patients on HOE 901 compared to 25% of patients on NPH. With BG <2.0mM, it was reported in 3.4% of both groups. There were small differences between HOE 901 and NPH with respect to BG throughout the day. Fasting BG was lower with HOE 901 but bedtime and 3:00 am BG tended to be lower with NPH.

The following subgroup factors were found to have no effect on change in HbA1c, FBG or symptomatic hypoglycemia: age, sex, or pubertal stage.

Two patients on HOE 901 had unexplained urticaria. One patient on NPH had an unexplained anaphylactic reaction that required treatment with hydrocortisone. Injection site events were reported in 9 patients (5.2%) on HOE 901 and 5 patients (2.9%) on NPH, but in no instance was the event severe enough to discontinue the medication. Measurements of antibodies to HOE 901 and human insulin did not disclose any clinically meaningful information. A predefined criteria of 20% absolute increase in binding of labeled ligand (Bound/Total) disclosed two patients on HOE 901 and five patients on NPH. The most dramatic case (———), both with respect to maximal binding and the rise in binding, illustrates that changes in insulin binding have little if any clinical consequence (see table below). This patient was treated with NPH insulin once daily and showed little change in insulin dose or GHb despite the dramatic rise in insulin binding. The rise in binding is itself difficult to explain because this patient had been on NPH insulin before the study:

	Baseline	Endpoint
Insulin binding(-B/T):		
HOE 901	10.6	55.6
Human insulin	11.4	56.2
Total insulin dose, units	66	72
GHb,%	9.7	9.0

Of patients who were negative for E Coli antibodies at baseline 5.8% of HOE 901 patients and 3.6% of NPH patients became positive at endpoint. There was one patient in each group who was positive at baseline who became negative.
There were no deaths during the study. There were 7 patients (4%) on HOE 901 and 18 patients (10.3%) on NPH who required hospitalization. In 3/7 patients on HOE 901 and 11/18 patients on NPH, the hospitalization was because of acute complications of diabetes.

One patients on HOE 901 and three patients on NPH developed wbc counts under 3GG/L. Ketosis/ketoacidosis was reported in one (0.6%) patient on HOE 901 and 3 (1.7%) patients on NPH. No case was attributed to study medication.

Summary:

HOE 901 and NPH give similar results with respect to glucose control in children with type 1 diabetes, as measured by changes in HbA1c and episodes of hypoglycemia. The only clinically important finding is that patients transferring from twice daily NPH to once daily HOE 901 can expect a switch from basal to regular insulin of about 10% of their total dose.

Phase 2 studies.

Phase 2 studies were conducted in the United States (2002) and Europe(2003). Combining both data sets, a total of 593 patients with type 1 diabetes received HOE. The study treatments lasted lasted four weeks and used change in FPG as the primary efficacy measure. The mean starting dose of HOE 901 or NPH insulin was about 21 units. The mean fell one unit in HOE 901 patients and remained unchanged in NPH patients at endpoint. Mean baseline FPG was about 12 mM. The change at endpoint was – 2.36 mM for HOE 901 and – 0.34 mM for NPH (p=0.0001). In study 2002, it was found that patients previously on multiple doses of basal insulin developed nocturnal hypoglycemia when switched to once daily HOE 901. This led to a small reduction in the dose of HOE 901. In study 2003 and phase 3 studies, investigators were advised to reduce the dose of HOE 901 at their discretion.

Because studies 2002 and 2003 lasted only four weeks and FPG (not GHb) was the measure of efficacy, the Sponsor has stated that they are not adequate to establish a claim

of efficacy. However, the results of these studies are consistent with the results of phase 3 studies done later.

APPEARS THIS WAY
ON ORIGINAL

Studies in patients with Type 2 diabetes

Study 3006

This was a 28-week open label study in patients who had been taking insulin for at least three months and had not used oral hypoglycemic agents for at least three months. Patients were stratified according to whether they had been taking once daily or multiple daily doses of basal insulin. They were then randomized to HOE 901 once daily or NPH once daily or twice daily. This means that patients, who had previously taking once daily basal insulin, continued to take once daily basal insulin (NPH or HOE 901). Patients who had previously taking multiple doses of basal insulin received either once daily HOE 901 or twice daily NPH. Regular insulin was given in accordance with how the patients had uised regular insulin previously. NPH and regular insulin were supplied as Lilly Humulin. HOE 901 was supplied in 5 ml vials.

Fundic photographs were taking at baseline and endpoint. Patients with EDTRS level > 43 received as additional photograph at 12 weeks. A clinically relevant change was defined as: development of EDTRS > 61, three step or greater progression of EDTRS or macular edema.

The treatment group consisted of 259 patients each on HOE 901 and NPH. 28 HOE 901 patients withdrew and did 21 NPH patients. Mean age was 59.3 years. Mean duration of diabetes was 13.7 years, 8.3 years on insulin. 20 % basal insulin once daily, 79 % twice daily, 1.7% three times daily. Mean BMI was 30.5. There were 60% male. Mean values at baseline were GHb 8.5%, FPG 10.9mM, FBG 9.2 mM.

Differences in the change in insulin dose at endpoint were accounted for by patients who had prior multiple doses of basal insulin. The mean dose of basal insulin in these patients at baseline was about 50 units. At endpoint the change in basal insulin dose was – 3.1 units HOE 901 patients and + 7.6 units for NPH patients. This rise in NPH is somewhat unexpected because most patients were simply continuing the insulin regimen they had been taking before the study. Mean regular insulin dose at baseline was about 22 units. There was a rise of 10.6 units for HOE 901 patients and 5.4 units for NPH patients. Thus the differences in basal insulin dose was partially made up for differences in regular. The total insulin dose rose 9.7 units for HOE 901 patients and 14.6 units for NPH. Among patients previously on once daily basal insulin, mean basal and regular insulin rose in HOE 901 and NPH groups. The increase in total insulin dose was 11 units in HOE 901 patients and 7 units in NPH patients. Looking at all patients without regard to previous

regimen, there was a mean rise in total insulin dose of 10 units in patients on HOE 901 and 13.1 units in patients on NPH.

The primary efficacy analysis was change in GHb. At baseline mean GHb was about 8.55%. By 8 weeks there was a change of -0.32 in HOE 901 patients and – 0.59 for NPH patients. This yields a treatment effect in favor of NPH of 0.27 (p=0.0006). At endpoint the treatment effect was 0.17 in favor of NPH but of borderline significance (p=0.055). The reduction in GHb was greater for patients who were on NPH once daily or twice daily.

Symptomatic hypoglycemia confirmed by BG<2.0 mM was reported by 6.6% of patients on HOE 901 compared to 10.4% (p=0.055) patients on NPH. All symptomatic hypoglycemia was 61.4% for HOE 901 and 66.8% for NPH (p=0.18). Nocturnal hypoglycemia documented by BG<2.0 mM was 5% of HOE 901 patients and 4.6% of NPH patients. But all nocturnal hypoglycemia occurred less frequently with HOE 901 than with NPH (31.3% vs 40.2% p=0.016). There were only seven subjects who reported severe hypoglycemia. One HOE 901 patients reported three events and six NPH patients each reported one event. Asymptomatic hypoglycemia confirmed by BG <2.8 mM was more frequent for patients on HOE 901 than NPH (8% vs 3.5% p=0.03) for months 2-enpoint but for the entire study the difference (7.7% vs 4.6%) was not statistically different. Fasting plasma and blood glucoses were not different between the treatment groups

Plasma C peptide levels were 0.6 nM (about 2 ng/ml) at baseline. There was no change to endpoint with either treatment. Fasting serum insulin fell slightly in HOE 901 patients (- 3.72) and rose slightly in NPH patients (2.18) from mean baseline of about 200 pM (about 30 uU/ml). But the analysis was complicated by " several extreme values." In response to an inquiry, HMR explained that free insulin was not extracted prior to immunoassay (amendment 2). Thus, the "extreme values" described by HMR probably reflect the presence of endogenous antibodiesin the serum of these insulin-treated patients

Injection site reactions were reported in 7.7% of HOE 901 patients compared to 3.9% of NPH patients. There were two death in HOE 901 patients, both due to CVA's. There were three deaths in NPH patients, 2 episodes of sudden death and one death due to metastatic cancer (4 weeks after study ended). AE's requiring hospitalization occurred in 24 patients on HOE 901 and 23 patients on NPH. Skin rash/pruritis was reported by 4 HOE 901 patients and 6 NPH patients.

Insulin antibody binding (% bound/total) was about 17% at baseline. At endpoint there was a small fall in HOE 901 patients and a slight rise in NPH patients. The net difference was 2.27% with respect to labeled HOE 901 (p=0.0002) and 2.64% with respect to labeled human insulin (p=0.0001). In response an inquiry, HMR indicated binding in normal human serum could be as high as 10% and that patients values were not corrected for non-specific binding. The small difference in binding between patients treated with

HOE 901 and NPH is probably not meaningful. A 20% absolute rise in binding was reported in 3 HOE 901 patients and 2 NPH patients. One patient on each treatment had a rise in binding from about 30% at baseline to about 65% at endpoint. Despite this rise in binding, total insulin dose and GHb declined in both patients. Conversion from negative to positive for E Coli antibodies were reported in 3 HOE 901 patients and 2 NPH patients.

The was a statistically significant difference (p=0.028) in the number of patients who experienced a three or greater step progression of retinopathy in patients on HOE 901 16/213 (7.5%) vs NPH 6/220 (2.7%). The Sponsor states that this difference is "unexpected, unexplained and may be the result of statistical chance." This issue is discussed in detail in a later section

There were no significant differences in serum lipids. Body weight gained 0.4 kg in HOE patients compared to 1.4 kg in NPH patients (p=0.0007). Four patients in each group developed clinically relevant EKG changes.

Summary: Glycemic control was very similar in patients treated with HOE 901 and patients treated with NPH. The NPH-treated patients had a slightly greater reduction in GHb levels but also tended to use more insulin. Weight gain was small but significantly greater with NPH than with HOE 901. I attribute these small differences to the fact that the study was unblinded and patients may have been more willing to increase the dose of their previous medication, NPH insulin, than of the new insulin, HOE 901. A significant progression of retinopathy was reported in patients on HOE 901 compared to those on NPH.

APPEARS THIS WAY
ON ORIGINAL

3002- Long-term study in patients with type 2 diabetes, many of whom were insulin-naive

This was a 52 week open label study of HOE 901 vs NPH, each given once daily at bedtime, in patients with type 2 diabetes previously on oral hypoglycemic agents with or without once daily insulin. Inclusion criteria were type 2 diabetics ages 40-80, history of diabetes for at least 3 years, on a stable antidiabetic regimen for at least three months. Patients could be insulin naïve or on a combination of once daily insulin plus a sulfonylurea. GHb was between 7.5 and 12%, BMI, 40. Patients were excluded if they had used regular insulin on month before screening or had had surgical treatment of diabetic retinopathy within three months of screening.

Of 570 treated patients (289 on HOE 901 and 281 on NPH) there were 54% men, mean age 59.5 years, mean duration of diabetes of 10.3 years, 8.3 years of oral agents and mean BMI 29.1. At baseline the ITT population had a mean GHb of 8.9%, FPG 12.4 mM, FBG 9.8 mM. All but 4% were on a SFU. 20% were on SFU alone, 41% on SFU plus

metformin and 25% on SFU plus insulin. Oral agents remained constant throughout the trial. Patients previously on insulin had a median dose at baseline of 20 units, which rose 4 units at endpoint. Insulin naïve patients started at median dose of 10 units, which rose 8 units at endpoint. The median insulin doses were the same for HOE 901 and NPH patients. In the HOE group there were 222 naïve patients and 67 insulin-pretreated patients. In the NPH group there were 204 naive patients and 77 insulin-pretreated patients.

GHb at baseline was 9.06% for HOE 901 patients and 8.88 for NPH patients. This baseline inequality was of marginal statistically significance (p=0.06). The change from baseline was – 0.46 for HOE 901 patients and – 0.38 for NPH patients (NS). Analysis based on whether patients were on insulin previously made no difference in the comparison between treatments except that insulin naïve patients had a mean fall in GHb during the treatment, - 0.65 and –0.63 for HOE and NPH patients respectively, while insulin pretreated patients showed a small rise 0.31 and 0.42. Although there was no difference between the treatment groups with respect to change in GHb, the somewhat lower baseline value in NPH patients meant that the endpoint GHb was slightly lower as well. The endpoint GHb for HOE 901 patients was 8.5% vs 8.3% for NPH patients. Thus one would expect a tendency for more hypoglycemia in the NPH groups simply on the basis of this small baseline inequality (see below)

There were no significant differences between HOE 901 and NPH with respect to symptomatic hypoglycemia, except that for cases occurring month 2 and after, the frequency of patients with at least one episode was lower for HOE 901 than for NPH (19.2% vs 26.1%, p=0.05). This difference was totally attributed to the insulin-naïve patients For the entire study, the frequency of all symptomatic hypoglycemia for naïve patients on HOE 901 was 33.3% vs 42.1% in NPH patients (p=0.04). For insulin-pretreated patients, the frequency was 40.3% and 35.1% for HOE 901 and NPH respectively (p=0.21). Only about 5% of cases of hypoglycemia were confirmed with BG<2.0 mM. There were significant differences between the two treatments with respect to reporting of nocturnal hypoglycemia. For the entire treatment period, 12.1% of HOE 901 patients compared to 24.2 NPH patients reported hypoglycemia (p=0.0002). Again this difference was due the insulin naïve patients where the frequency was 9.9% with HOE 901 compared to 24% for NPH (p=0.0001). The frequency among insulin-pretreated patients was 19.4 and 24.7% (NS). The number of reports confirmed by BG<2.0 mM was very low, 2/35 HOE 901 patients and 3/68 NPH patients. 5 subjects on HOE 901(1.7%) and 3 subjects on NPH (1.1%) had at least one episode of severe hypoglycemia. Asymptomatic hypoglycemia with BG< 2.8 mM was reported in 11/289 (3.8%) subjects on HOE 901 and 10/281 (3.6%) subjects on NPH. The higher frequency of hypoglycemia in NPH patients is consistent with data from self-glucose monitoring. The mean fasting values (reduction from baseline) tended to be lower (0.27 mM, p=0.08) with NPH than with HOE 901 at week 36 but not at other weeks. 3 am-glucose was also tended to be lower (reduction from baseline) with NPH than HOE 901 (0.38 mM p=0.11) at week 8, but not at later times.

Fasting C peptide levels were about 0.9 nN in both groups at baseline. There were nonsignificant reductions at endpoint of 0.14 and 0.09 in HOE 901 and NPH patients respectively. Insulin levels were not different between the treatment groups at baseline or throughout the study. The text says that the immunoassay measures HOE 901 and its metabolites with 50% cross-reactivity. For this reason, and also the presence of antiinsulin antibodies in insulin-treated patients, the validity of these data is suspect.

Subgroup analysis showed that obese patients (BMI > 28) had a better response in GHb to HOE 901 than NPH (-0.42 vs - 0.11 p=0.024), although the baseline values however were somewhat higher in HOE 901 patients than NPH (9.09 vs 8.95) Among non-obese patients there was no difference between the two treatments. Among obese patients the reduction in FBG tended to be better than NPH (-2.62 mM vs – 2.29 mM p= 0.08); the baseline value was 10.1 mM in both cases. Despite the somewhat greater reduction in glycemia, the frequency of nocturnal hypoglycemia was less for HOE 901 than NPH (9.5% vs 22.2% 0=0.006). All symptomatic hypoglycemia was not different (32.5% and 37.3%). There were 5 (3%) cases of severe hypoglycemia with HOE 901 and 2 cases (1.3%) on NPH. Among non-obese patients there was a also tendency (p=0.095) for less nocturnal hypoglycemia with HOE 901 (16%) vs NPH (27%).

Safety

There were seven on-treatment deaths, 1 on HOE 901 and 6 on NPH. Four patients on HIE 901 and six on NPH had life-threatening events. None of these appear to be treatment related. In 5 HOE 901 patients and 7 NPH patients, adverse event was listed as a cause of withdrawal. In one HOE 901 patient there was a hypoglycemic reaction. In one NPH patients there was an injection site reaction. Withdrawal due to hyperglycemia was recorded in one patient in each group.

Rash and/or pruritis was recorded in 7 patients on HOE 901 and 5 on NPH. Injection site reactions were reported in 9 HOE 901 patients and 11 NPH patients. A larger rise in antiinsulin antibodies, occurred insulin-naïve patients treated with NPH vs HOE 901 (absolute increase of about 7% vs 3%) However, the high values at baseline (about 7 % in these insulin naïve patients) is due to non-specific binding. Of 274 E Coli antibody-negative patients, 7 became positive on HOE 901. Of 262 E coli antibody- negative patients, 3 became positive on NPH.

Progression to proliferative retinopathy (PDR) occurred in 2 patients on HOE 901 and none on NPH. Progression from no retinopathy to non-PDR occurred in 8.4% of HOE 901 patients and 14 % of NPH. Clinically significant macular edema (CSME) developed in 1.8% of HOE 901 patients and 2.4% of NPH patients. By fundic photography three step retinopathy progression was observed in 5.9% of HOE 901 patients and 9.1% of NPH patients (p=0.3). By fundic photography, CSME developed in 26/233(11.2%) patients on HOE 901 compared to 14/214 (6.5%) of patients on NPH (P=0.10). CSME more frequently with HOE 901 than NPH in patients insulin-naïve patients (14% vs 4 % p=0.002) but the situation was reversed in insulin-pretreated patients (1.9 vs 12.7%, p=0.04).

There were no changes in serum lipids. There was a small mean weight gain in both treatment groups. This was about 0.5 kg greater in insulin-naïve patients than in the group as a whole. Insulin-naïve patients gained 2.57 kg on HOE 901 and 2.34 kg on NPH. in insulin-naïve patients. Four patients on HOE 901 developed wbc counts under 3 GG/L One patients on NPH developed ALT over 1000.

Summary: This study has not identified any major differences between HOE 901 and NPH insulin.

Phase 2 studies in type 2 diabetes

A total of 475 patients with type 2 diabetes were treated with HOE 901 in phase 2 studies 2004 (Conducted in Europe and South Africa), 2005 (USA) and 2006(Europe). Treatment with HOE 901 or NPH lasted four weeks. Most patients were insulin naïve and used insulin in combination with oral agents. In comparison to NPH, the mean dose of HOE was higher at endpoint, but the difference was not great. There were no differences in change in FPG or frequency of hypoglycemia. The results of these preliminary trials are considered supportive of the phase 3 studies.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

Major Review Issues:

Biopharm issues:

A PK/PD study was done using the glucose clamp technique (section 6H). Normal volunteers were given 0.4 units/kg of HOE 901, NPH or ultralente, each on two occasions. Glucose was infused to prevent hypoglycemia. The amount of glucose required to keep the blood glucose levels constant at about 81 mg/dl was used as a glucodynamic measurement. This is a valid way to measure insulin action in man. Insulin blood levels were measured as well. However, the assay cannot distinguish exogenous insulin (including HOE 901 which is said to have 50% immunoreactivity of human insulin) from endogenous insulin. Determination of blood levels of the drug requires a correction for endogenous insulin secretion using C peptide levels. For this reason the PK data should be taken as an approximation. Indeed, the text acknowledges that there was one outlier whose C peptide levels did not fall and whose data were excluded on that basis. PK results (using mean and median figures) are shown in the table below. The C max is achieved at 4 hours with NPH and 12 and 13 hours with HOE 901and ultralente respectively. The C max and AUC are highest with NPH. I do NOT take this to mean that NPH has greater bioavailablity for two reasons. The first is that the collection stopped at 24 hours which may be too early for the long acting drugs. Second, the problem of endogenous insulin makes it difficult to distinguish low levels of exogenous insulin from baseline. This is less of a problem with NPH because of its sharper peak than with HOE 901 or ultralente. The C max and AUC are higher with ultralente than with HOE 901 despite the slightly longer T max with ultralente. If one were to accept these data literally, one would have to conclude that HOE 901 has reduced bioavailability relative to ultralente. I do not believe this to be the case because the PD measure (glucose infusion rate, GIR) did not suggest that HOE 901 was less bioavailable than ultralente. A more likely explanation is that the immunoassay underestimated the levels of HOE 901 and its active metabolites.

	PK immunoreactive insulin			PD GIRmg/kg
	AUC 0-24	C max uU/ml	Tmax hours	GIR 0-24
HOE 901	178	11	12	2700
NPH	278	21	4	3000
Ultralente	206	16	13	2300

Results of the intrasubject CV shown in the table below illustrate that NPH is the least variable with respect to PD and HOE 901 and ultralente are about the same. Ultralente is

more variable by PK criteria, but I do not accept the validity of the methodology for the reasons described above.

Intrasubject CV	PD GIR (0-24)	PK AUC (0-24)	C max
HOE 901	32%	14%	28%
NPH	19%	16%	15%
Ultralente	38%	70%	67%

In summary, HOE 901 shows delayed absorption relative to NPH insulin. Its absorption properties are similar to ultralente. Given the limited validity of the PK measurements, and their inconsistency with PD measurements, no comparative statements should be allowed in the label.

Glycemic control:

Glycemic control is roughly the same with either NPH and HOE 901. Patients switched from NPH to H0E 901 should expect to reduce their dose of basal insulin about 10-20% to prevent hypoglycemia and increase the premeal regular (or lispro) insulin accordingly. Otherwise the two treatments appear largely indistinguishable. That HOE 901 is given only once daily, as opposed to NPH, which is best given twice daily, would appear to offer an advantage. However, NPH insulin can be mixed with regular insulin and injected together in the same syringe. Therefore some patients would require fewer injections if switched to HOE 901 while others would require more. A commonly used regimen in patients with type 1 diabetes is regular insulin before meals and NPH twice per day. Patients on this regimen receive three injections daily, two of regular mixed with NPH before breakfast and dinner and a third injection of regular alone before lunch. HOE cannot be mixed with regular insulin, so the total number of insulin injections in patients on HOE 901 plus pre-meal regular would be four. A problem yet to be faced is what would happen if a patient mixed HOE 901 with regular insulin and injected the mixture despite warnings not to. I would expect that the lower pH of HOE 901 would cause the regular insulin to come out of solution, and greatly delay its absorption. I believe such patients to be at risk of delayed hypoglycemia, which would be greatly exacerbated if they took additional insulin to compensate for the perceived lack of effect of the mixture.

Hypoglycemia was defined in this NDA in many ways: all symptomatic, severe symptomatic, nocturnal, confirmed by glucose < 2.8mM, confirmed by glucose < 2.0mM, or asymptomatic. The primary analyses was HOE 901 to NPH (all patients). But subgroup analysis compared HOE 901 to NPH once daily and HOE 901 to NPH twice daily. Separate analysis were done for episodes during the first month of the trial and those that occurred during months 2-6. Additional subgroup analysis was performed to examine the effect of previous insulin regimen (once daily or multiple basal insulin) on development of hypoglycemia during the trials. Given the large number of comparisons it is not surprising that some of them appeared to be statistically significant. Even more important when considering comparisons is that the trials were unblinded and that all but the most severe episodes of hypoglycemia are subject to reporting bias. This is particularly true for nocturnal hypoglycemia which HMR explained in amendment 2, would include "signs and symptoms recognized by a partner while the subject was

asleep" . While strange behavior during sleep, as reported by a bed-partner, might be used by an experienced clinician as evidence for nocturnal hypoglycemia, it should not used as evidence to support a labeling claim. In addition, investigators were advised in advance that the dose of HOE 901 should be reduced in patients switching from multiple doses of NPH in order to prevent nocturnal hypoglycemia.

Even leaving aside the limitations of methodology, and taking the results at face value, the Sponsor does not make a convincing case that HOE 901 is better than NPH with respect to hypoglycemia. Pooling results from studies 3001 and 3004 show a statistically significant reduction in severe hypoglycemia and nocturnal hypoglycemia in patients previously on once daily basal insulin but not in patients previously on multiple doses of basal insulin. Given the fact that NPH has peak activity at about 4-8 hours, it is not surprising that giving the entire dose of NPH at one time might result in some episodes of hypoglycemia, but that this problem could be avoided by splitting the dose. These results (pooled 3001 and 3004) only confirm what is largely known or expected, that giving NPH only once daily is not optimal. It is also worth noting that study 3005 (use with lispro) did not confirm a decrease in severe hypoglycemia with HOE 901. A more consistent finding (studies 3001, 3004, 3005 and 3006) is that asymptomatic hypoglycemia is reported LESS frequently in patients previously on multiple doses of basal insulin who are continued on NPH rather than being switched to HOE 901. The importance of hypoglycemic unawareness should not be underestimated. In the DCCT trial there were no deaths directly attributable to hypoglycemia, but there were three deaths (including one bystander) due to auto accidents in which hypoglycemia may have played a role.

Based on the biopharm data, the absorption profile of HOE 901 (Tmax=12 hrs) is approximately the same as ultralente (Tmax=13 hrs). Zinman et al has recently reported (Diabetes Care, 22, 603, 1999) no significant differences in glycemic control between NPH and ultralente in a 12-month **blinded** study. Therefore, patients who desire a long-acting insulin can get good results with ultralente. [redacted]

Retinopathy:

The concern that HOE 901 might exacerbate diabetic retinopathy stems from a body of evidence for the role of IGF 1 in proliferative retinopathy and the reports in the NDA (section 5:vol.018) showing that that HOE 901 has more IGF-like activity than does human insulin. Using cultured cardiomyoblasts [redacted], displacement of radiolabeled IGF-1 by 1nM unlabeled IGF-1, HOE 901 or insulin was about 42%, 15% and 4% respectively. From the full competitive binding curves I estimate that the relative affinity of HOE 901 for the IGF receptor is roughly five times that of human insulin. In cultured human osteosarcoma cells, Froesch estimated that HOE 901 had eight times the receptor binding affinity and five times the mitogenic activity of human insulin. Arg(B31Arg(B32) insulin was somewhat more potent than HOE 901 itself. Also using

osteosarcoma cells, Trub found that HOE 901 had 14 times the receptor binding affinity and six times the mitogenic affinity. Taken together, these results raised the possible that treatment of diabetic patients with HOE 901 would lead to more IGF-related events than treatment with human insulin. For this reason , DMEDP requested that retinal exams be incorporated into the phase 3 trials.

The potential role of IGF1 in the development of diabetic retinopathy has recently been reviewed by Burgos et al (Diabetes Care vol 23, January 2000 pps 80-83).The fear that IGF 1 could exacerbate diabetic retinopathy stems from the observation of patients with severe diabetic retinopathy whose disease regressed after pitutiary ablation. High levels of IGF1 have also been reported in patients with rapidly progressive proliferative retinopathy (Merimee et al. NEJM 309, 527-1983). The trials of IGF1 for the treatment of type 1 diabetes seemed to confirm with this finding (Thrailkill et al Diabetes Care, 22, 585, 1999). A three step or greater increase in retinopathy was found in 16/151(11%) IGF-1 treated patients and 0/48 patients treated with insulin only. The finding occurred in 6% of patients treated with 80 ug/kg IGF1 and 13% treated with 120-140 ug/kg. Progression of retinopathy occurred primarily in young women with little or no background retinopathy. There were three patients who had neovascularization of the optic disc and received laser coagulation during the 12 week trials, who had only background retinopathy initially. All three were on the higher doses of IGF1. Optic disc swelling was present in all three of these patients and in 16 other patients on 1GF 1. Possible optic disc swelling was present in 7 other IGF1 –treated patients but no placebo-treated patients. The Sponsor contended that this transient worsening of retinopathy in IGF –treated patients, particular optic disc swelling, was due to improved glycemic control, a phenomenon which has been reported in several trials. However, DMEDP was not convinced that the worsening in retinopathy was due to improvement in HbA1c. While recognizing that mild pregression of retinopathy had been reported in other trials (DCCT for instance), we were unable to find examples of patients receiving laser therapy for proliferative retinopathy developing during the first 12 weeks of a trial. Indeed, the rapid progression in these three patients treated with high dose IGF 1 appeared ominously similar to the cases with increased IGF1 levels reported by Merimee et al.

Progression of retinopathy found in diabetic patients treated with IGF 1 was found in type 1 patients only. Evaluable information is available in only a small number of patients with type 2 diabetes. Three step progression was found in 1/10 patients on placebo, 0/10 patients on 80 ug/kg and 0/4 patients on 160 ug/kg.

The finding of progression of retinopathy in patients treated with HOE 901 seems superficially reminiscent of the findings with IGF-1. But I am not convinced that the findings reported with HOE 901 in this NDA are related to the findings with IGF1. The most important difference is that progression of retinopathy with IGF1 occurred in patients with type 1 diabetes but not type 2 diabetes. The opposite was the case with HOE 901. Also, while it appears that HOE 901 and its metabolites have more IGF1 activity than insulin, it must be born in mind that HOE 901 has much less IGF1 activity than does IGF1 itself. The estimates for its activity from different laboratories are

discordant. Froesch reported that HOE 901 had about 5% the binding and 22% the mitogenic activity of IGF1 itself. While Trub reported less than 0.1% the receptor binding activity but over 50% the mitogenic activity. Even if one assumed a high estimate that HOE 901 had 30% IGF-1 activity, it is not clear that giving HOE 901 would elevate total IGF-1 activity in a way that is physiologically meaningful. Although IGF1 levels were not measured in the HOE 901 studies, patients with type 2 diabetes are not known to have IGF1 deficiency. Giving a small amount of IGF-1 activity in the form of HOE 901 would not be expected to have a large effect. The dose of IGF-1 given in the diabetes trials described above (120-140 ug/kg) was nearly ten times higher than the dose of HOE 901. On the other hand, the physiologically important concentration of IGF-1 is much lower than the total concentration because of the presence of IGF binding proteins. Assuming that HOE 901 (like insulin) is not bound to these proteins, the IGF1- like activity of a small dose of HOE 901 might be greater than what would be predicted from in vitro assays in which the binding protein were absent.

In summary, I believe the reasons to be concerned that HOE 901 might exacerbate retinopathy are not compelling. Nevertheless, the fact that the finding occurred in a controlled clinical trial requires that HMR address the issue definitively (see phase 4).

Immunological issues:

Mean insulin binding in serum of insulin-naïve type 2 diabetic patients was reported to be about 7%. That the binding was so high in patients who had never been treated with insulin suggested that the data had not been corrected for non-specific binding. In response to an inquiry, HMR indicated that changes in serum binding to radiolabeled HOE 901 and human insulin was determined using [redacted]
Binding to normal control human serum could be as high as 10% (amendment 2).

I believe that this high non-specific binding probably reflects precipatation of aggregated ligand, labeled degradation products and trapping of labeled ligand in the precipitate. Taking an absolute increase of 20% (roughly twice non-specific binding) to be possibly significant, as was done in the phase 3 protocols, avoids the need to deal with non-specific binding, and is a perfectly acceptable way to screen large numbers of samples. There were several patients in both treatment groups who had large increases in insulin binding without any obvious clinical consequences. These data would have answered the Division's concern that HOE 901 may be more antigenic than NPH during long-term use. However, [redacted] based on small changes in binding in insulin naïve patients. In order to make this claim they would have had to use more sophisticated methodology. [redacted] But it does not separate antibody-bound ligand from aggregated ligand, degradation products and/or radioiodinated material bound to impurities. It would have been preferable to use a second antibody to precipitate only human immunoglobulin. In addition, sera found to be

"positive" on initial testing should have been retested following preincubation with an excess of unlabeled insulin to displace labeled insulin from specific binding sites. The residual binding that occurs in the presence of unlabeled insulin is the non-specific which should have been subtracted from the total. Because these techniques were not used, the difference in binding between naïve patients treated with HOE 901 and those treated with NPH is within the range of non-specific binding. It is therefore inappropriate to claim that HOE 901 is less immunogenic than NPH.

Potential for patient error:

HOE 901 is a clear solution and can therefore be confused for short acting insulins. Other forms of basal insulin are suspensions. The potential for error due to confusing different preparations was demonstrated in trial 3005 in which hypoglycemia was attributed to Lispro being confused with HOE 901 on six occasions and with NPH only once. HMR should come up with distinctive packaging to discourage confusing HOE 901 with other insulin products or mixing HOE 901 with other insulins.

Labeling issues:

The raison d'être for HOE 901 is its unique absorption characteristics. There is little else to distinguish it in the clinical trials. However, the proposed label gives little detailed discussion of the absorption characteristics [redacted] Since the trials were unblinded, no superiority claims should be allowed. The label should be revised with a change in emphasis:

The diagram of the structure of HOE 901 should include arrows or bars to indicate the major active metabolites.

Fig 1 – The lack of statistical data leaves the impression that the peak action of NPH at 6 hours is reproducible from patient to patient. Data on inter-intrapatient variability should be included. Insulin blood levels should also be given in a figure

[redacted] should be deleted, [redacted]

Metabolism -

[redacted]

Table 1 and accompanying text – The table is constructed in such a way to give the [ ] is not acceptable. The frequency of asymptomatic hypoglycemia is greater with HOE 901 than with NPH in some trials but this result does not appear in the table. Because change in GHb was the major efficacy variable, I cannot object to showing this result in a table. Insulin doses can be given in the same table ——— should go out entirely. Otherwise, ALL pertinent comparisons should be included in tables, even if they do not favor HOE 901. ——— should not be included unless confirmed by plasma determinations in the laboratory. ——— should also be shown in a table if the Sponsor insists on presenting ——— in a table. Otherwise the finding can be discussed under Precautions.

[ ]

Retinopathy – No mention is made whatever of progression of retinopathy in one trial and increased macular edema in another. I tend to agree with the Sponsor that these findings were not meaningful. But to omit them entirely is another example of selective reporting and is not acceptable.

Phase 4

The two major safety issues are concerns about the progression of retinopathy and the consequences of inadvertent mixing. To address the retinopathy issue, the Sponsor should perform a large simple trial in patients with type 2 diabetes with little or no background retinopathy. It should compare once daily HOE 901 with twice daily NPH and should be powered to detect a two-fold increase in three step progression of retinopathy over one year with 90% power. The need to include retinal evaluation was faxed to HMR on November 23, 1999 as part of comments on protocol 4002. ———

[ ]

Summary and recommendation:

Once daily HOE 901 gives roughly the same glycemic control as twice daily NPH. This may translate into fewer injections in certain patients depending on whether or not they mix insulins. HOE 901 cannot be mixed with regular insulin [redacted] The vials should not be approved until HMR comes up with distinctive packaging to discourage mixing. The packaging will need to be such that HOE 901 can be identified easily without reference to the printing on the label so that it will not be confused with other insulin products. [redacted]

Because the trials were unblinded, no claim of superiority to NPH insulin should be allowed. An increase in the progression of retinopathy was reported in one study of type 2 diabetes, but was not observed in other studies. The question should be evaluated in a phase 4 trial.

The label requires substantial revision. The pharmacology section should be expanded and the clinical trials section shortened. Any claims of superiority over NPH insulin should be deleted. The retinopathy findings should be included.

The NDA is approvable pending these changes.

/S/

Robert I Misbin MD
HFD 510
NDA 21081
January 21, 2000
(revised January 24, 2000)

/S/ 1/27/00

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION /S/ 10-21-99

TO *(Division/Office)*: Wiley Chambers, HFD-550

FROM: HFD-510 (Division of Metabolic and Endocrine Drug Products) Julie Rhee

October 21, 1999	IND NO.:	NDA NO.: 21-081	TYPE OF DOCUMENT: Clinical Amendment	DATE OF DOCUMENT: October 18, 1999
NAME OF DRUG: Lantus™(insulin glargine injection)	PRIORITY CONSIDERATION:	CLASSIFICATION OF DRUG:	DESIRED COMPLETION DATE: November 19, 1999	

NAME OF FIRM: Hoechst marion Roussel, Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ■ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER:	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER:

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Please see the attached e-mail from Dr. Misbin. Thank you.

cc: Original NDA 21-081
HFD-510/Div. Files

SIGNATURE OF REQUESTER: /S/ 10-21-99	METHOD OF DELIVERY (Check one): ■ MAIL ☐ HAND
SIGNATURE OF RECEIVER:	SIGNATURE OF DELIVERER:

JAN 12 2000

Medical Officer's Review of NDA 21-081
Ophthalmology Consultant

NDA #21-081		Submission:	10/18/99
M.O. Consult Review #1		Review completed:	1/12/00

Proposed trade name:	Lantus
Generic name:	Insulin glargine injection
Development name:	HOE 901
Sponsor:	Hoechst Marion Roussel, Inc. 10236 Marion Park Drive Kansas City, MO 64134-0627 (816) 966-6794
Pharmacologic Category:	Insulin analog
Proposed Indication(s):	Once-daily subcutaneous administration in the treatment of patients with type 1 or type 2 diabetes mellitus who require basal (long-acting) insulin for the control of hyperglycemia.
Consult Requested:	Consultation concerning the development of retinopathy

APPEARS THIS WAY
ON ORIGINAL

Summary of Relevant Retinal Findings from Studies 3001, 3002, 3004 and 3006

	Study 3001		Study 3004		Study 3002		Study 3006	
	HOE 901	NPH	HOE 901	NPH	HOE 901	NPH	HOE 901	NPH
Retinopathy ≥3 Step Progression (photographic evaluation)	5%	3%	3%	4%	6%	9%	8%	3%
Visual Acuity – Patients with doubling of visual angle	2%	2%	3%	2%	2%	4%	5%	3%
Macular edema	7%	8%	1%	1%	11%	7%	3%	2%
Retinal Adverse Event	6%	4%	10%	10%	3%	2%	22%	25%
Development of Proliferative Diabetic Retinopathy	2%	3%	2%	4%	2%	2%	4%	2%

Study 3001 Open label, randomized study with 28 week treatment phase in type 1 diabetics
Study 3002 Open label, randomized study with 52 week treatment phase in type 2 diabetics
Study 3004 US, open label, randomized study with 28 week treatment phase in type 1 diabetics
Study 3006 US, open label, randomized study with 28 week treatment phase in type 2 diabetics

Reviewer's Comments:

1. *There is a statistically significant higher percentage of patients with a 3 step progression in the HOE 901 Group compared to the NPH group in study 3006. There are no other significant differences were observed in the key retinal evaluations.*

2. *All of the studies are of short duration with respect to the evaluation of diabetic retinal changes. To properly evaluate diabetic retinal changes, the study duration should be at least 3 years.*

3. *Both European studies (3001 and 3002) had a high percentage of photographs which were not available for evaluation (37% and 32% respectively). Three step progressions cannot be accurately determined in the absence of fundus photographs.*

12 Conclusions

Of the two studies with the highest ability to accurately determine 3 step progressions in the diabetic retinopathy scale score, one of the studies demonstrated the study drug to have a higher frequency of progressions.

13 Recommendations

It is recommended that an additional study be conducted to evaluate the risk of retinopathy progression. The study should include retinal photographs of all patients at baseline and at every 3-6 months in follow-up. The study duration should be at least 1 year in duration although ideally, 3 years would be more convincing. The evidence of a significant problem with respect to diabetic retinopathy is not sufficiently strong to preclude approval of the drug product at this time. It is recommended that the additional study be submitted as a Phase 4 study.

/S/

Wiley A. Chambers, M.D.
Supervisory Medical Officer, Ophthalmology

cc: NDA 21-081
HFD-510
HFD-510/CSO/Rhee
HFD-510/MO/Misbin
HFD-105
HFD-550/Consult File
HFD-550/MO/Chambers

APPEARS THIS WAY
ON ORIGINAL